

Claims 27-34 have been rejected under 35 U.S.C. § 101 on the basis that the claimed invention is inoperative and therefore lacks utility. The examiner asserted that there is no suggestion in the application that any of the utilities disclosed in the application are attainable or even practical. Several references were cited by the examiner as providing evidence that antibodies are not successful therapeutic agents. The examiner stated that in view of these references, one of ordinary skill in the art would not accept Applicant's claimed utility without a showing of convincing objective evidence of therapeutic or diagnostic utility. This rejection is traversed.

Enclosed is a copy of a declaration by Dr. Robert Lifely which was submitted in parent application Serial Number 08/155,864. As Dr. Lifely explains in his declaration, CHO-glycosylated antibodies have been administered to patients suffering from disorders such as rheumatoid arthritis and lymphoma. Reports of these tests have been published in the journal *The Lancet* and copies of the papers are provided with Dr. Lifely's declaration¹. The declaration also notes a report by Dr. Geoff Hale summarizing data obtained from clinical testing of a patient suffering from autoimmune vasculitis conducted at the MRC/Wellcome Therapeutic Antibody Centre in Cambridge, England. These various reports show that CHO-glycosylated antibodies have

¹Copies of all attachments referred to in Dr. Lifely's declaration are enclosed for completeness, although some, such as those referring to the use of the antibodies of the present invention for the treatment of forms of cancer, are not directly relevant to the claims pending in the present application.

been administered to human patients suffering from T-cell mediated disorders with efficacious results and that the present invention clearly has utility.

Even absent the data provided in Dr. Lively's declaration, the references cited by the examiner do not support this conclusion that the present invention lacks utility. The examiner's comments concerning the Waldmann reference appear to be based upon the statement in the introduction of the paper at page 1657 which bridges the left- and right-hand columns, where the author says:

Despite the wide-ranging interest, the "magic bullet" of antibody therapy that has been the dream of immunotherapists since the time of Paul Ehrlich has proved to be elusive.... Furthermore, the initial use of unmodified murine monoclonal antibodies in human patients with cancer was disappointing. This statement, as it stands in the context of a review article, is not inaccurate, but it is misleading to take it out of context and apply it to the present invention.

The quoted passage is concerned with the possible use of monoclonal antibodies in the treatment of cancer. Initial results of antibody administration in humans tended to be obtained from patients where the antibody had been used as a last resort, i.e., patients with very advanced cancers. Results from such patients cannot be generalized into a conclusion that the whole therapeutic concept is ineffective.

The examiner's summary of the Waldmann paper is an unduly harsh assessment of the overall comments and tenor of the reference. Certainly the path of development of therapeutic monoclonal antibodies has not been completely smooth, and some antibodies that have looked promising in initial trials, especially in the field of cancer therapy, subsequently have proved to be less effective than originally hoped. As Waldmann makes clear, however, researchers have shown that monoclonal antibodies can be effective therapeutic agents. He notes in his introduction that monoclonal antibodies have been "applied clinically to the diagnosis and therapy of cancer and the modulation of the immune response to produce immunosuppression for treatment of autoimmune and graft versus host diseases and for the preparation of allograft rejection." He further notes that such antibodies have been applied clinically against various viruses and bacteria. He goes on to state that such antibodies have been proposed for therapy of myocardial infarction, reversal of drug toxicity and for fertility control. He then summarizes both recent advances and setbacks in research involving monoclonal antibodies. His conclusion certainly is an optimistic one, however; he states that

[s]ince the development of monoclonal antibody technology, the medical community has applied these agents to in vivo diagnosis and therapy of human disease. Recent advances in linkage of toxins and isotopes to monoclonal antibodies and in genetic engineering of antibodies has led to reduced

immunogenicity and has improved effector function, thus providing new potential for the prevention of allograft rejection and for the treatment of neoplastic, infectious and autoimmune diseases.

A person of ordinary skill in the art would not conclude from this paper that antibodies have no usefulness.

With regard to the Harris paper cited by the examiner, it should be kept in mind that this paper is not a scientific review but a report of a conference the objective of which was to promote various commercial organizations involved in the engineering of antibodies. This, combined with the fact that at least one of the authors is the founder of such a company, does not suggest that the article is likely or intended to provide a balanced scientific view. The statement from the paper quoted by the examiner is misleading in the conclusions that the examiner attempted to draw from it. It is not true that rodent monoclonal antibodies cannot be used therapeutically in humans and a number of such antibodies are in clinical trials, including OKT3 and an anti-IL2 (anti-tac) antibody. The extent to which rodent antibodies can be used in humans depends very much on the disease or disorder being treated and the effect that it is desired to achieve. Rodent antibodies can be quite acceptable in therapy in humans.

The Osband et al. paper is a look at "Problems in the investigational study and clinical use of cancer immunotherapy" and all comments made by the authors must be understood to be

made in the context of cancer therapy. This paper thus has no relevance to the presently claimed invention.

The examiner further noted that the Dillman reference provides that monoclonal antibody therapy has met with only limited success in humans. As with the Osband et al. reference, the focus of this reference is on monoclonal antibodies for treating cancer, so all of Dillman's comments must be taken in the context of cancer therapy. The reasons why immunotherapy of cancer is not analogous to other types of therapy already have been discussed above. Even so, Dillman does not support the examiner's pessimistic view. Rather, he gives an upbeat assessment of monoclonal antibody therapy. More specifically, he says that

the current status of monoclonal antibody therapy in cancer is one of continued promise....Those who feel that the efforts of the past 10 years indicate that this approach is a failure are overlooking the complexities of the challenge and the progress which has been made.

The Hird et al. reference also cited by the examiner is yet another reference which focuses on the use of antibodies in cancer therapy. The passage quoted by the examiner, that "[t]he data obtained from mouse studies are useful but cannot be directly translated to apply to the human situation," is made not only in the context of cancer therapy but in the context of human tumor xenografts in nude mice. These tumors tend to be difficult

to treat and, in any case, the nude mouse has no immune system, so that the results can hardly be directly applicable to immunotherapy in man.

Hird et al. further provide a list of supposed problems with antibody therapy. Even if these are real problems, they can apply only to cancer therapy and have no bearing on the use of an antibody in, for example, therapy of autoimmune conditions.

The final reference cited by the examiner in support of his rejection under § 101 is a paper by Curti. Again, this paper has no relevance to the present invention; its title is "Physical Barriers to Drug Delivery in Tumors." There is no discussion or suggestion in the paper regarding the administration of antibodies to patients suffering from a T-cell mediated disorder.

In view of the foregoing discussion, Applicant respectfully submits that the references cited by the examiner do not support his assertion that the claimed invention has no utility. He further submits that the results of *in vivo* antibody administration presented herewith clearly show the utility of the present invention.

The specification has been objected to, and the pending claims rejected, under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure. Specifically, the examiner asserted that the Applicant has not disclosed how to use the antibody as a pharmaceutical or therapeutic agent. The examiner stated that in view of the unpredictable nature of the

method claimed, it would require undue experimentation to obtain the claimed invention. This rejection is traversed.

Applicant respectfully submits that the present application does enable one of ordinary skill in the art to administer the antibodies to effect treatment of different disorders and diseases. Page 10 of the specification, for instance, sets forth a list of diseases and disorders which can be treated through the administration of a CHO-glycosylated antibody. The application teaches that a generally suitable dosage of antibody is within the range of 1 - 100 mg for an adult human patient and preferably is within the range of 1 - 10 mg, usually administered daily for a period of 1-30 days. In the clinical studies reported in the publications and declaration by Dr. Lifely cited above, the antibodies were administered in dose regimens that fall within these guidelines. Finding the optimum dose for a particular patient may require routine experimentation on the part of the physician, but the guidelines presented in this application provide sufficient information to enable one to tailor a treatment regimen without engaging in undue experimentation.

Claims 27-34 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. The examiner noted that claim 27 should have an "a" after the word "treating". This rejection has been obviated by the amendment to claim 27 set forth above.

Claim 1 has been rejected under 35 U.S.C. § 102(b) as anticipated by either Cabilly et al. or Bodmer et al. This rejection has been obviated by the cancellation of claim 1 from the application. Applicant reserves the right to file a continuation application directed to the subject matter of claim 1.

Claims 27-34 were provisionally rejected under the judiciously created doctrine of obviousness-type double patenting as unpatentable over claim 38 of co-pending application Serial No. 08/155,864. The examiner noted that the only difference between the claims of the two applications was the scope of the treatment method being claimed. The examiner further asserted that a timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome this rejection.

This rejection is a provisional obviousness-type double patenting rejection as Applicant has not yet received an indication from the Patent Office that either the present application or the '864 application contains allowable subject matter. Upon an indication of allowable subject matter in these applications, Applicant will file a terminal disclaimer.

Claims 27-34 were rejected under 35 U.S.C. § 103 as unpatentable over Cabilly et al. or Bodmer et al. in view of Benjamin et al. or Riechmann et al. The examiner asserted that Cabilly et al. teach a CHO-glycosylated form of an antibody, citing column 10, first full paragraph, of the Cabilly et al. patent. Bodmer et al. were cited as teaching the use of CHO

cells to produce chimeric B72.3 antibodies and that these antibodies are superior to murine antibodies. Bodmer et al. further were cited as teaching that antibodies can be used for the treatment of cancer. The examiner acknowledged that neither of these two references teach a method for treating a cell-mediated disorder that is an autoimmune disease. The Benjamin reference, however, was cited as teaching the induction of tolerance by monoclonal antibody therapy using an anti-CD4 antibody. The examiner stated that the induction of tolerance would treat a T-cell mediated disorder that is an autoimmune disease. Riechmann et al. were said to teach the reshaping of an antibody which recognizes the CDw52 antigen for therapeutic use. A person of ordinary skill in the art was said to have been motivated to produce the antibodies of either Benjamin et al. or Riechmann et al. in CHO cells and that it thus would have been obvious to apply the teachings of either Cabilly et al. or Bodmer et al. to those of either Riechmann et al. or Benjamin et al. to obtain a CHO glycosylated antibody useful in a method for treating a mammal suffering from a T-cell mediated disorder. This rejection is traversed.

Enclosed with this response are copies of declarations by Dr. Scott Crowe and Dr. Geoffrey Hale that have been submitted to the Patent Office in connection with the prosecution of parent application 08/155,864. Reference will be made to these two declarations in the discussion below.

As an initial point, Applicant notes that the Cabilly et al. reference was cited against the claims of pending parent application Serial Number 08/155,864 under 35 U.S.C. §§ 102 and 103². The § 103 rejection was withdrawn following the response Applicant filed in which the declaration by Dr. Lifely referenced above was enclosed. In addition, at an interview held with the examiner in February of this year in connection with the '864 application, the examiner agreed to withdraw the § 102 rejection in view of a lack of specific teaching in the reference of the use of a CHO-glycosylated antibodies for therapeutic purposes.

In columns 8-10 of the patent, Cabilly et al. discuss host cell cultures and vectors. They state that the vectors and methods disclosed in the patent are suitable for use in host cells over a wide range of prokaryotic and eukaryotic organisms. They describe microorganisms useful as hosts, then go on to state that cultures of cells derived from multicellular organisms also can be used as hosts. Examples of useful cell lines are said to include "VERO and HeLa cells, Chinese hamster ovary (CHO) cell lines, and W138, BHK, COS-7 and MDCK cell lines." (column 10, lines 21-24).

The sentence quoted above is the only reference in the patent to CHO cells as hosts. As the examiner himself has acknowledged, the patent does not teach that CHO-glycosylated antibodies can be administered as a therapeutic agent. Cabilly

²The § 103 rejection was based upon a combination of the Cabilly et al. and Riechmann et al. references.

et al. generally state that their recombinant antibodies are useful in diagnosis and therapy. It is not at all clear from the patent whether Cabilly et al. even were suggesting that CHO-glycosylated antibodies might be useful therapeutically. The patent certainly does not contain any teaching that CHO-glycosylated antibodies could be administered to patients suffering from T-cell mediated or autoimmune disorders, including vasculitis, multiple sclerosis, rheumatoid arthritis, or graft vs. host disease, as an effective treatment.

The fact that an antibody can be expressed in a particular host cell does not necessarily mean that the antibody will be an effective therapeutic agent when administered to a patient. As the declarations enclosed with this response make clear, the prior art as a whole has recognized that glycosylation is an essential feature of an antibody. Differences in glycosylation can affect its biological activity through, for example, altered Fc receptor binding and/or complement activation, as well as circulatory lifetime, immunogenicity and antigenicity *in vivo*. Glycosylation also is influenced by such factors as species-, tissue- and cell-type. One skilled in the art simply could not have predicted at the time of the invention that an antibody with CHO glycosylation would be effective as a therapeutic simply because the same antibody had been shown to have therapeutic utility when produced, for example, in myeloma cells. As also is explained in Dr. Lifely's and Dr. Hale's declarations, the scientists who carried out the initial *in vivo* experiments with

CHO-glycosylated CAMPATH-1H had no expectation that the antibody would, in fact, prove to be effective *in vivo*.

Dr. Lifely further explains that in view of the *in vivo* data that now have been generated using CHO-glycosylated antibodies, he would expect other antibodies produced in CHO cells to have similar and appropriate glycosylation. The glycosyl transferase present in CHO cells would be the same regardless of the particular antibody being produced and one of ordinary skill in the art, in light of the data generated by the Applicant, would expect them to glycosylate any antibody in a similar manner.

Dr. Crowe's declaration provides that it now has been found that not only are CHO-glycosylated antibodies effective in humans but the nature of CHO glycosylation is such that the antibodies produced in CHO cells are particularly well suited for therapeutic use in humans.

The other primary reference cited, Bodmer et al., was said to teach the production of antibodies in CHO cells. The examiner also referred to a statement on page 3 of the Bodmer et al. application that antibodies can be used diagnostically and for the treatment of cancer.

As an initial point, the statement on page 3 to which the examiner referred is merely part of the general background section of the application. The statement does not refer to antibodies produced in CHO cells. Indeed, since the statement refers to the state of the prior art, it necessarily concerns antibodies produced in cells other than CHO cells.

Bodmer et al. focus on the production of a humanized antibody having an antigen binding site wherein at least the complementarity determining regions (CDRs) of the variable domain are derived from the mouse monoclonal antibody B72.3. The application provides that the antibody can be produced in "a eukaryotic cell, most preferably a mammalian cell, such as a CHO cell or myeloid cell." (p. 7) Statements in the application concerning possible therapeutic uses of the murine B72.3 antibody and its humanized forms (e.g., paragraph bridging pp. 4 and 5) do not specify production in CHO cells or any particular cell type. In the examples provided in the application, Bodmer et al. illustrate the production of a chimeric B72.3 antibody in CHO cells. The only utility for this antibody provided in the application, however, is tissue targeting after the antibody was labeled with ^{125}I . Moreover, Bodmer et al. do not teach or suggest the administration of a therapeutically effective amount of any antibody, much less a CHO-glycosylated antibody, nor does the reference provide any guidance as to what such amounts would be.

Thus, neither of the primary references teaches that a CHO-glycosylated antibody can be considered a therapeutic agent. Furthermore, neither of the secondary references cited by the Examiner compensates for the deficiencies of the two primary references. The Benjamin et al. reference does teach the administration of a monoclonal antibody in mice to induce tolerance, but there is no teaching or suggestion in the

reference that an antibody produced in CHO cells can be administered to treat a T-cell mediated disorder. Similarly, although Riechmann et al. teach that a reshaped anti-CDw52 antibody can be administered for therapeutic purposes, they do not teach or suggest that reshaped antibodies produced in CHO cells can be effective therapeutically. The antibodies discussed in the Riechmann et al. paper were produced in lymphoid cells.

To summarize, in view of the teachings of the prior art, taken as a whole, as set forth in Dr. Lifely's declaration, and further amplified in the declaration by Dr. Crowe, persons skilled in the art at the time of the present invention did not have a reasonable expectation that CHO-glycosylated antibodies would be effective therapeutic agents. A discussion in the Bodmer et al. application--and mere suggestion in the Cabilly et al. patent--that recombinant antibodies could be produced in a wide variety of host cells, including CHO cells, does not render obvious the present discovery that CHO-glycosylated antibodies can be administered to patients suffering from a T-cell mediated disease or disorder as an effective therapeutic treatment.

None of the references, therefore, taken singularly or in combination, render obvious the presently claimed invention.

In view of the foregoing amendments and discussion,
Applicant respectfully submits that the claims of this
application are in condition for allowance.

Respectfully submitted,

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